No. 19-2011

IN THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CONCERT PHARMACEUTICALS, INC.,

Appellant,

v.

INCYTE CORPORATION,

Appellee,

KATHERINE K. VIDAL, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office,

Intervenor.

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board, No. IPR2017-01256

NONCONFIDENTIAL BRIEF OF APPELLEE INCYTE CORPORATION

J. Derek McCorquindale
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
1875 Explorer Street
Suite 800
Reston, VA 20190-6023
(571) 203-2700

Trenton A. Ward
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
271 17th Street, NW
Suite 1400
Atlanta, GA 30363-6209
(404) 653-6400

Thomas L. Irving
Mark J. Feldstein
Jason L. Romrell
C. Collette Corser
Drew D. Christie
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001
(202) 408-4000

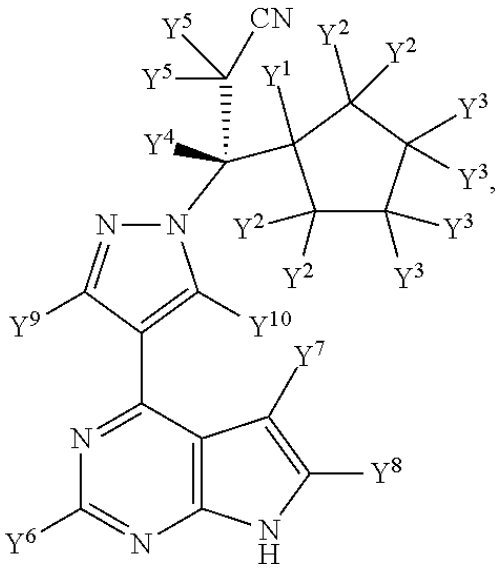
Counsel for Appellee

October 6, 2022

EXEMPLARY PATENT CLAIM AT ISSUE

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8, Y^9 and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 2019-2011

Short Case Caption Concert Pharmaceuticals, Inc. v. Incyte Corporation

Filing Party/Entity Incyte Corporation

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box.** Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: October 6, 2022

Signature: /s/ Mark J. Feldstein

Name: Mark J. Feldstein

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities.	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities.
☐ None/Not Applicable	☒ None/Not Applicable	☒ None/Not Applicable
Incyte Corporation		

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Christopher Lee McDavid	formerly Finnegan, Henderson, Farabow, Garrett & Dunner	
Maureen D. Queler	formerly Finnegan, Henderson, Farabow, Garrett & Dunner	
Michael John Flibbert	Finnegan, Henderson, Farabow, Garrett & Dunner	
Rachel Lauren Emsley	formerly Finnegan, Henderson, Farabow, Garrett & Dunner	
Michele M. Simkin	Foley & Lardner	
Stephen B. Maebius	Foley & Lardner	

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☒ None/Not Applicable ☐ Additional pages attached

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☒ None/Not Applicable ☐ Additional pages attached

TABLE OF CONTENTS

CONFIDENTIAL MATERIAL OMITTED

The material omitted on pages 21 and 67 describes the purported isotopic purity of Concert's CTP-543 compound. To Incyte's knowledge, Concert treated the foregoing material as confidential information during the *inter partes* review.

TABLE OF AUTHORITIES

Cases **Page(s)**

Constitutional Provisions

Statutes

Other Authorities

STATEMENT OF RELATED CASES

No appeal in or from the same *inter partes* review proceedings was previously before this or any other appellate court.

Counsel is aware of no case pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal.

INTRODUCTION

Each claim of Concert's U.S. Patent No. 9,249,149 ("the '149 patent") covers analogs of the previously known and FDA-approved compound ruxolitinib with hydrogen substituted for deuterium—"the smallest structural change that can be made," Appx2919—at known metabolic sites. Carefully weighing an extensive record, the Patent Trial and Appeal Board found that each claim would have been obvious. Concert now attempts to recast the Board's fact-bound conclusions as legal errors and replace them with its own pinched view of the record. This Court should reject Concert's attempt to manufacture legal issues on appeal. The Board correctly applied the law and thoroughly explained the basis for its decision, which was well supported by substantial evidence.

Concert does not dispute that a skilled artisan would choose ruxolitinib as a lead compound to make structurally similar compounds. Appx21. Not only was ruxolitinib the first FDA-approved treatment for myelofibrosis, it was also known to be effective against autoimmune disorders, including alopecia areata.

Instead, Concert tries to portray deuteration as a "notoriously unpredictable" endeavor, insisting in the face of all evidence that a skilled artisan had no motivation to deuterate ruxolitinib because "there was no way to predict" what deuteration would do for a given compound. Blue Br. 1. But Concert's prior-art "Precision Deuterium Chemistry Backgrounder" highlighted exactly how skilled

artisans could improve safety, tolerability, and efficacy—all while greatly reducing R&D risk, time, and expense—by deuterating compounds with known efficacy against clinically validated targets at their metabolic hotspots. Appx23-24; Appx30. And its own CEO confirmed in a prior-art publication that skilled artisans would have expected deuterated ruxolitinib compounds to have the same selectivity and potency as their hydrogen analogs. Appx23-24; Appx27-28. Considering the entire record, the Board made detailed findings that the claimed deuterated compounds and ruxolitinib are sufficiently similar to create an expectation that they would have similar properties. Appx24; *see also* Appx27-28.

The Board did not, as Concert contends, rely on an "abstract motivation to deuterate *any* molecule with known metabolic 'hot spots.'" Blue Br. 2-3. What the Board actually did was weigh extensive evidence—including published metabolic data—identifying specific sites on ruxolitinib's cyclopentyl ring as the very metabolic hotspots targeted by the prior art as ideal for deuteration. Appx21-28. While ruxolitinib was associated with hematological side effects in blood cancer patients predisposed to such issues, it was generally safe and well tolerated in healthier subjects. And even if serious side effects occurred, the Board found that skilled artisans would have understood how to mitigate them through dose modification. Appx24-26.

Concert also alleges that the Board erroneously "inferred" a motivation from "some" similar properties while ignoring that "pharmacokinetic properties" were "not known." Blue Br. 3. But the motivation to make a structurally similar compound cannot be avoided simply by pointing to some "unpredictability" in an unclaimed property; if that were true, then there could never be a motivation to make a compound that required some "verifi[cation] through testing." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). But in any event, the Board independently found that a skilled artisan would have been motivated to deuterate ruxolitinib at its metabolic hotspots to achieve the potential pharmacokinetic benefits disclosed in the prior art, including improved safety, tolerability, and efficacy. Appx23-24; Appx31-32; Appx1739-1740.

Concert's challenge to the Board's "reasonable expectation" findings also fails as a matter of law. According to Concert, the Board was obligated to consider unclaimed pharmacokinetic properties in its analysis. Blue Br. 3. But that is not the correct inquiry—obviousness requires "a motivation to combine accompanied by a reasonable expectation of achieving *what is claimed* in the patent-at-issue." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (emphasis added); *see also* Appx29-33. None of the challenged claims here recite any pharmacokinetic properties. And there is no dispute that achieving what is claimed—deuterated ruxolitinib molecules—was well within the

skill in the art and routine. Appx30-31. Yet even applying Concert's erroneous standard, the Board also correctly found—consistent with its motivation findings—that skilled artisans would have had a reasonable expectation that deuterated ruxolitinib may display superior pharmacokinetic properties. Appx31-32; Appx22-28. This Court has never required "guaranteed" success, only a "reasonable expectation of success." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014).

Concert's complaints about the Board's treatment of its alleged secondary indicia fare no better. Blue Br. 3-4. The "unexpected results" for its CTP-543 compound are neither unexpected nor significant differences in kind. Appx33-35. And the Board found that CTP-543 did not satisfy a long-felt, unmet need not because it lacked FDA approval, Blue Br. 4, but because Concert had not shown that CTP-543 actually treated alopecia areata with a lower dose and fewer side effects than ruxolitinib, Appx35-37. Moreover, none of Concert's alleged secondary indicia are commensurate with the scope of any challenged claim.

Taken together, the Board's detailed findings—each supported by substantial evidence—cement both a motivation to deuterate ruxolitinib at its metabolic hotspots and a reasonable expectation of success. This Court should affirm.

STATEMENT OF THE ISSUES

The issues presented are:

1. Whether substantial evidence supports the Board's finding that a skilled artisan would have been motivated to deuterate ruxolitinib at its metabolic hotspots.

2. Whether substantial evidence supports the Board's finding that a skilled artisan would have had a reasonable expectation of successfully making the compounds claimed in the '149 patent.

3. Whether substantial evidence supports the Board's finding that Concert's alleged objective indicia did not support nonobviousness.

4. Whether Commissioner Hirshfeld violated the Appointments Clause or the Federal Vacancies Reform Act in denying Concert's request for review.

STATEMENT OF THE CASE

A. Scientific and Factual Background

1. Deuterium Substitution

Like many elements, hydrogen exists in different isotopes. Its most common isotope, known as "protium" or "hydrogen," has a nucleus consisting of a single proton. Appx2377. Another hydrogen isotope, known as "deuterium," has a nucleus consisting of one proton and one neutron. Appx2377. While having a larger mass, deuterium is essentially identical to hydrogen in terms of size and

electronic properties. Appx135-136; Appx1428(2:15-20). Thus, replacing one or more of a compound's hydrogen atoms with deuterium (known as "deuteration") does *not* affect its pharmacodynamics (i.e., its biochemical potency and selectivity for the target receptor). Appx1477 ¶55; Appx1428(2:15-20); Blue Br. 7. This was well known in the art. Appx2380; Appx2919; Appx2406; Appx2785; Appx6016(97:4-18). Concert's CEO publicized in 2009 that "[a]t Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'" Appx2406.

Because deuterium (D) has nearly twice the mass of hydrogen (H), it forms significantly stronger bonds with carbon (C). Appx1472-1473 ¶¶50-52. And because more energy is required to break a stronger C-D bond, deuteration can lead to differentiated pharmacokinetics affecting a compound's ADME (Absorption, Distribution, Metabolism, and Excretion). *Id*. For instance, deuteration can slow drug metabolism and, therefore, its clearance. This concept—known for decades—is called the kinetic isotope effect ("KIE"). *See, e.g.*, Appx1471-1477 ¶¶49-56; Appx2377-2379; Appx2404.

The KIE was known to impart several advantages. Appx1472-1473 ¶50. Concert's 2007 "Precision Deuterium Chemistry Backgrounder" describes these advantages, including how deuteration can provide "[b]etter tolerability through

reduction of overall dose and C_{max}"[1] and "[e]nhanced efficacy by increasing bioavailability, AUC[2] and C_{min} with minimal impact on C_{max}." Appx1739-1740. The Concert Backgrounder taught that these changes could produce "NCE's [new chemical entities] with improved safety, tolerability and efficacy." Appx1739. And the Concert Backgrounder's teachings were consistent with myriad prior-art references. *See, e.g.*, Appx2404; Appx5525-5526; Appx5548-5549.

While there may be some academic debate over which step in the catalytic cycle causes the KIE for a given compound, *see* Blue Br. 8-9, the practical effect—reduced metabolism—is the same. Appx747-750. A "conservative analysis," Appx10573-10574(92:12-93:2), by Incyte's expert, Dr. Reider, found that deuterium modification slowed the rate of metabolism in approximately 79% of more than 180 unique compounds contained in 33 prior-art references. Appx6488 ¶99. Additionally, Dr. Reider considered deuterated compounds featured in original research published by Dr. Guengerich, another Incyte expert. Dr. Reider's conclusion? Of these 33 unique compounds, KIE was reported for 31 (94%). Appx6488-6489 ¶¶99-101.

[1] "C_{max}" is the maximum plasma concentration of a drug after administration, while "C_{min}" is the minimum plasma concentration.

[2] AUC stands for "area under the curve," a common pharmacokinetic parameter that expresses the total plasma concentration of a drug.

As early as the 1980s, skilled artisans would have known that "[t]he attraction of specific deuterium substitution as a parameter in drug design is based on the facts that not only is the replacement of one or a few hydrogens in a drug molecule by deuterium *the smallest structural change that can be made* but also such a change will have negligible steric consequences or influence on physicochemical properties . . . ." Appx2919 (emphasis added); *see also* Appx136-145; Appx1471-1487 ¶¶49-62. By 2012, at least three companies were dedicated to deuterating known compounds. Appx1477-1487 ¶¶56-63. As one CEO put it, "[t]he easiest way to find a drug is to start with one." Appx2406.

While the FDA may, under current regulations, treat a deuterated version of an existing drug as a "new chemical entity," *see* Blue Br. 14, deuteration does not impact selectivity or potency, meaning that deuterated drugs were known to perform *at least* as well as their hydrogen analogs. Appx1503-1504 ¶¶91-93; Appx2406; Appx6016(97:4-18); Appx1739. Indeed, deuterium substitution bypasses much of the early work required in creating a clinically viable compound, which "[g]reatly reduce[s] R&D risk, time and expense," and allows for "[r]apid phase 1 proof-of-concept." Appx1739; *see also* Appx30; Appx1491-1492 ¶¶72-74.

2. Ruxolitinib

a. Ruxolitinib Was Known to Safely Treat Multiple Conditions, Including Alopecia Areata

Ruxolitinib is a chemical compound that affects Janus kinases 1 and 2 (JAK1 and JAK2) signaling proteins, which mediate hematopoiesis and immune function. Appx1729; Appx1428-1429(2:53-3:6); Appx21. A dysfunctional JAK1/JAK2 response can lead to certain diseases; ruxolitinib inhibits those overactive proteins. Appx5465. At the time of the '149 patent's June 2012 priority date, ruxolitinib was a clinically established drug and the first FDA-approved treatment for myelofibrosis. Appx145-146; Appx1487-1488 ¶¶63-65; Appx1706-1728. And ruxolitinib was in clinical trials for the treatment of other conditions, including "essential thrombocythemia, pancreatic cancer, prostate cancer, breast cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma and psoriasis." Appx1429(3:3-6).

The prior art also taught JAK inhibitors, including ruxolitinib, as a treatment for alopecia areata ("AA"). Appx146; Appx734-735; *see also* Appx5716-5720. In 2010, a group from Columbia University filed a patent on the use of ruxolitinib to treat AA. Appx2407-2410; Appx6117-6118(70:21-71:2). The Columbia patent detailed the mechanistic underpinnings of JAK inhibition to treat AA—including identifying interferon gamma ("IFN-γ") as a key mediator—and disclosed the successful use of ruxolitinib and tofacitinib (another JAK inhibitor) in animal

models.[3] Appx6625-6629 ¶¶18-29; Appx2409-2410; Appx2417-2418; Appx2508-2509; Appx2538. Dr. Shapiro testified that in 2010 he attended an "AA Summit at Columbia University where [the use of] JAK inhibitors . . . for AA" was discussed. Appx6625 ¶19; *see also* Appx1518; Appx6103-6104(56:9-57:21).

According to Concert, a skilled artisan would have believed that slowing metabolism of ruxolitinib would increase serious side effects. Blue Br. 15-17. But Concert relies on hematological side effects in patients with myelofibrosis cancer—characterized by "abnormal blood counts (anemia, thrombocytosis or thrombocytopenia, and leukocytosis or leukopenia)"—who are predisposed to such effects. Appx6629-6630 ¶¶30-33 (citation omitted); *see also* Appx6099(52:3-24). In contrast, prior-art studies of ruxolitinib and other JAK inhibitors in populations comparable to AA reported no serious hematological side effects. Appx6630-6633 ¶¶34-41; Appx6673; Appx5472; Appx11176(37:6-24). And subsequent studies in AA patients confirmed that ruxolitinib produced only tolerable side effects. Appx6634-6636 ¶¶43-46; Appx7828-7829.

But even where they did occur, a skilled artisan would have known that side effects could be mitigated by dose modification. Appx25-26; Appx744-745; Appx5740(20:20-22:2); Appx8237; Appx8242-8246; Appx1709; Appx1713-1714.

[3] Ruxolitinib was also known as INCB018424. Appx5465.

This was true even for hematologically impaired myelofibrosis patients, where, as the Board recognized, adverse "events rarely led to treatment discontinuation . . . and *were generally manageable with dose modifications* . . . ." Appx25 (emphasis added) (quoting Appx9491); *see also* Appx5891-5893(64:18-66:15).

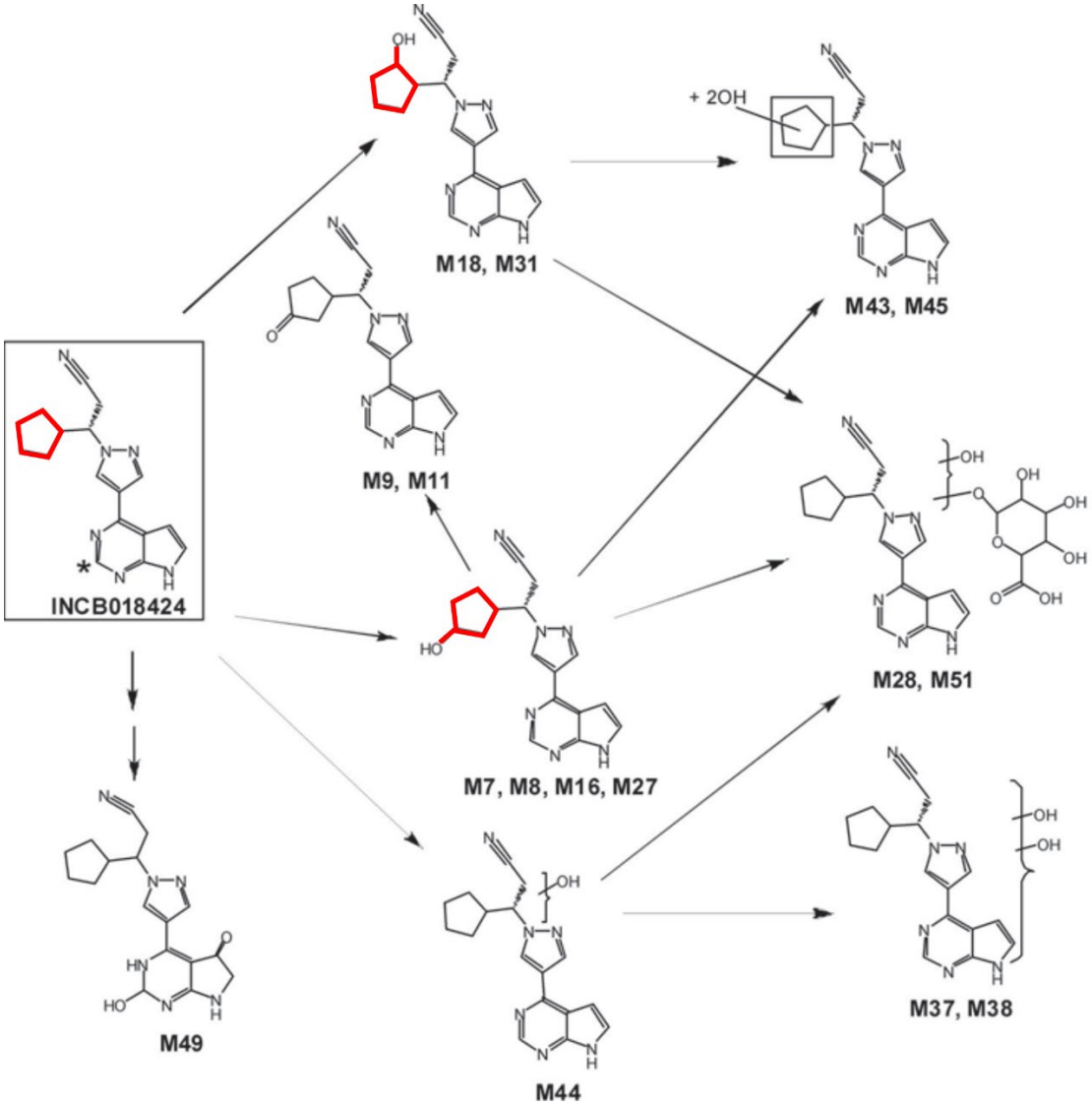
b. Ruxolitinib Was an Ideal Candidate for Deuteration

That ruxolitinib was a compound with "known efficacy and safety that address[es] clinically validated targets" alone made it a target for deuterium modification. Appx1740. But ruxolitinib further stood out from other FDA-approved drugs because its specific characteristics provided a high level of confidence that its metabolism would be slowed via the KIE. Appx746-747; Appx1500-1502 ¶¶83-88.

Concert contends that "[a]t least four variables" make it "difficult, if not impossible, to predict whether deuteration will result in a KIE for any *particular* drug compound." Blue Br. 7-8. Even setting aside that approximately 79% of the unique deuterated compounds of record showed a KIE, Appx6488 ¶99; *see supra* Section A.1, none of these alleged "variables" would have discouraged a skilled artisan from deuterating *ruxolitinib*.

Start with the fact that ruxolitinib had well-identified sites of metabolism that directed those of skill in the art where to deuterate. Appx1500-1502 ¶¶83-87;

Appx1525-1528 ¶¶133-136. As shown below, Shilling reported that the vast majority of ruxolitinib's metabolism occurred on its cyclopentyl ring.



Appx1734 (Shilling Figure 2 showing ruxolitinib (INCB018424) metabolism (major pathways annotated)); *see also* Appx1733-1736; Appx1489-1491 ¶¶68-70; Appx1500 ¶84. Some reactions—including N-dealkylation and aromatic hydroxylation not relevant here—generally produce a lower KIE and therefore are generally not good candidates for deuterium modification. Appx1504-1509 ¶¶94-

103. But alkyl groups, such as the methylenes on ruxolitinib's cyclopentyl ring, "are characterized by rather high intrinsic kinetic deuterium isotope effects," Appx2823, and "*almost always* [produced] at least some deuterium isotope effect," Appx1474 ¶53. This was well known in the art. Appx5784(64:1-10); Appx9201-9202(115:9-116:18); Appx9275-9276(189:12-190:16); Appx2902; Appx9019; Appx9854.

This intuitive strategy of targeting known "metabolic hotspots"—i.e., substituting deuterium at the locations subject to metabolism—was outlined in the Concert Backgrounder and was well known in the art. Appx1492-1500 ¶¶74-82; Appx1741. Unlike other compounds with dispersed sites of metabolism, the skilled artisan knew with exacting specificity where to modify ruxolitinib to slow its metabolism. *See* Appx751-752; Appx9324-9327(238:9-241:8).

Ruxolitinib's concentrated sites of metabolism also meant that the KIE was unlikely to be significantly affected by "metabolic switching" to minor (less than 5%) pathways. Appx160; Appx751; Appx1510-1511 ¶106; Appx1733-1734; *cf.* Blue Br. 10-11. And even where metabolic switching occurs, it only *reduces* the KIE—that is, there is still at least some slowing of metabolism relative to the parent compound. Appx5776-5778(56:20-58:3); Appx9210-9211(124:6-125:8); Appx1490-1491 ¶¶69-70. Nor would skilled artisans have been concerned about an increase in "undesirable or toxic metabolites," Blue Br. 10, as ruxolitinib had no

such metabolites, Appx1718-1719; Appx1734-1736; Appx5471-5472, and there had been no "reports of deuteration resulting in the formation of unique metabolites that were not also observed for the all-hydrogen analog," Appx1983.

Additionally, skilled artisans would have known that ruxolitinib was not subject to any factors that would potentially "mask" a KIE in patients (i.e., *in vivo*). Appx9131-9133(45:21-47:2); Appx9181-9187(95:15-101:16); Appx9224(138:11-21); Appx752-754; *cf*. Blue Br. 11. For instance, while the KIE can be masked where the clearance of a compound is high relative to hepatic blood flow, Appx5505, Drs. Guengerich and Ortiz de Montellano (Concert's declarant) agreed that a skilled artisan would *not* have expected such masking given ruxolitinib's "relatively low [clearance] at about 20% of hepatic blood flow," Appx7866; Appx9183-9187(97:8-101:16); Appx5855-5856(28:2-29:9); Appx5846(19:3-22); Appx5848(21:1-19); Appx5850-5853(23:5-26:18); Appx5856-5857(29:11-30:8).

Similarly, glomerular excretion and biliary clearance—both of which remove the compound from the body without it first being metabolized—and metabolism by conjugating enzymes, such as glucuronidation, can also potentially mask KIE. Appx5498-5499. Ruxolitinib, however, was not subject to any significant clearance by nonmetabolic processes, Appx7857-7858; Appx9182-9183(96:12-97:7); Appx9150-9151(64:7-65:9); Appx5868-5870(41:10-43:8), or direct

metabolism via conjugating enzymes, Appx5465-5466; Appx9194-9195(108:7-109:9).

While deuterium was expected to slow the metabolism of most compounds in *general*, the totality of the record underscores that this expectation was particularly high for ruxolitinib *specifically*. Appx746-752; Appx1504-1509 ¶¶94-103; *see also infra* Section C.2.

3. Prior-Art References

The Board based its obviousness conclusion on three primary references: Rodgers, the Concert Backgrounder, and Shilling.

a. Rodgers

U.S. Patent No. 7,598,257 ("Rodgers") is an Orange Book-listed patent that discloses and specifically claims ruxolitinib. Appx13-14; Appx166; Appx2644-2645; Appx1744; Appx1933(374:12-20). Rodgers discloses that ruxolitinib modulates JAK activity and is useful in treating JAK-related diseases. Appx1747(1:18-24); Appx13-14. Rodgers also teaches that compounds of its invention include those in which hydrogen is replaced with deuterium isotopes. Appx1762(32:13-17); *see also* Appx1522-1523 ¶130; Appx1525-1526 ¶133; Appx166-167.

b. The Concert Backgrounder

The Concert Backgrounder provides Concert's own publicly available description of its so called "Precision Deuterium Chemistry" platform. Appx1738-1743. Specifically, Concert explains the fundamental concepts and rationale underlying the use of deuterium to improve FDA-approved drugs. Appx14-19; Appx173-174; Appx1739-1742; Appx1491-1500 ¶¶71-82. Consistent with the art, the Concert Backgrounder discloses that "[d]euterium-substituted compounds retain their molecular shape and thus have selectivity and potency comparable to their hydrogen analogs." Appx1739.

The reference further teaches that due to the reduced metabolism of deuterated compounds, they have the potential to improve the safety, tolerability, and efficacy of "existing, validated drugs," including "[b]etter tolerability through reduction of overall dose and C_{max}." Appx1739-1740. It also explains that deuteration allows one "to rapidly create novel, differentiated compounds with substantially reduced R&D risk, time and expense." Appx1740. To achieve these benefits, the Concert Backgrounder teaches that compounds should be deuterated at their "metabolic 'hot spots,'" and provides an example demonstrating the predictability of that approach. Appx1741; Appx29-30.

c. Shilling

Shilling is a study of the metabolism, excretion, and pharmacokinetics of ruxolitinib. Appx1729-1737. It identifies ruxolitinib's metabolic hotspots, disclosing that the vast majority of ruxolitinib's metabolism occurs via hydroxylated oxidation at the 2- and 3-positions of the compound's cyclopentyl ring. Appx1734-1736. Consistent with Rodgers, Shilling teaches that ruxolitinib is a "potent, selective inhibitor of Janus tyrosine kinase 1/2 and the first investigational drug of its class in phase III studies for the treatment of myelofibrosis." Appx1729.

B. The '149 Patent

The '149 patent is directed to deuterated analogs of ruxolitinib. The specification does not describe or enable its claims with any data showing the effect of deuteration on *in vivo* pharmacokinetics. Rather, the specification points to Shilling's metabolic data for ruxolitinib. Appx1429(3:7-14). The only deuteration data in the specification is *in vitro* stability for three compounds deuterated at ruxolitinib's metabolic hotspots, which, as expected, exhibited increased stability (longer half-life) relative to their undeuterated parent compound. Appx1444-1445(34:22-35:18).

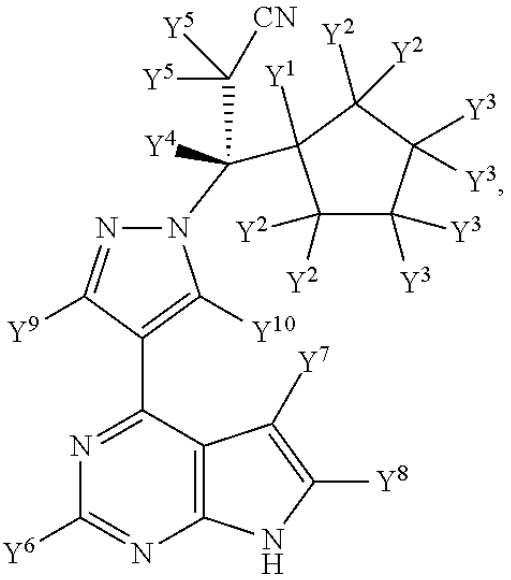
Nor does the specification describe or enable its claims with any clinical data, let alone data showing that deuterated ruxolitinib analogs are effective against AA.

Instead, relying on the well-understood principle that deuterated compounds will have the same pharmacodynamics as their parent compounds, the specification explains that ruxolitinib's deuterated analogs are useful in "treating a disease that is beneficially treated by ruxolitinib." Appx1437(20:57-61).

Challenged claims 1-15 recite deuterated analogs of ruxolitinib and pharmaceutical compositions thereof. None of the claims recite any particular use or application for the claimed compounds. Nor do they recite methods of treating AA, efficacy limitations, or clinical parameters. For example, claim 1 recites:

A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8 , Y^9 and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

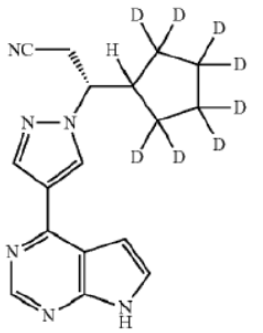
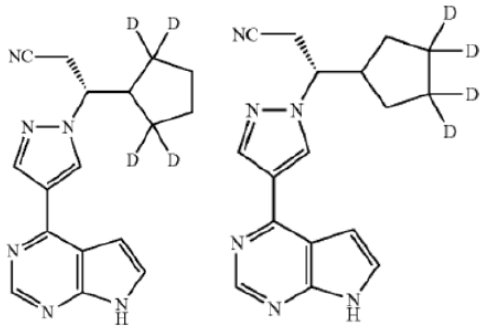
each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Appx1445(36:17-53).

All of the claims encompass at least one of three compounds deuterated at ruxolitinib's metabolic hotspots, shown below.

	
"octa-deuterated ruxolitinib"	"tetra-deuterated ruxolitinib"

Appx1464-1468 ¶¶33-40. Claims 1, 2, 5-7, 9, 10, 13, and 14 encompass "octa-deuterated" ruxolitinib, an analog with deuterium at the 2- and 3-positions of the cyclopentyl ring. *Id.*; Appx1445-1446(36:17-38:42). Claims 1-4, 6, 7, 9-12, and 14 encompass a pair of "tetra-deuterated" ruxolitinib compounds, one deuterated only

at the 2-position and the other only at the 3-position of the cyclopentyl ring. Appx1464-1468 ¶¶33-40; Appx1445-1446(36:17-38:42).

Octa-deuterated and tetra-deuterated ruxolitinib analogs differ only by the degree of deuteration of the cyclopentyl ring. Appx1464-1468 ¶¶33-40. Claims 8 and 15 each recite a pharmaceutical composition comprising a compound that reads on any of the three octa-deuterated and tetra-deuterated compounds above, and a pharmaceutical carrier. Appx1464-1468 ¶¶33-40; Appx1446(37:44-45, 38:43-44).

Concert asserts that it "recognized the potential for deuterated ruxolitinib to meet the long-felt need for a viable AA treatment," including "discover[ing] that ruxolitinib's inhibition of the IFN-γ pathway is much more potent than its inhibition of the EPO [erythropoietin] pathway." Blue Br. 18-19. But none of these alleged recognitions or discoveries are claimed in the '149 patent, much less disclosed.

C. CTP-543

All of Concert's and its Amicus's alleged "unexpected qualities" hinge on CTP-543, Concert's name for its octa-deuterated analog of ruxolitinib apparently having a specific isotopic purity. Blue Br. 19-23; *see also* Blue Br. 55-65; Amicus Br. 18-22. This compound is not remotely commensurate with the scope of the claims, and its properties are neither unexpected nor significant.

1. CTP-543 Is Not Commensurate with the Scope of the Claims

Concert's CTP-543 is the octa-deuterated analog of ruxolitinib with a purity data purity data isotopic purity. Appx9976 ¶10. But neither octa-deuteration nor a specific isotopic purity is commensurate with the scope of the '149 patent's claims. Appx733-734. Indeed, claim 1 covers *hundreds* of deuterated analogs. Appx6452-6454 ¶¶13-16. And even the narrowest claim still encompasses three distinct compounds. *Id.* Claims 3, 4, 11, and 12 do not even cover octa-deuterated ruxolitinib (CTP-543). *Id*.

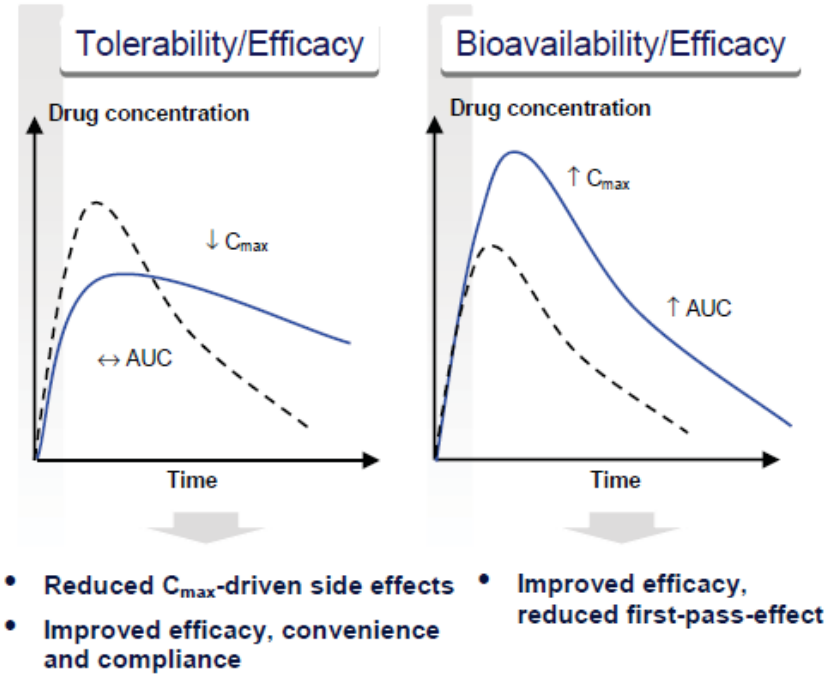
Moreover, none of the challenged claims recite any limitation of deuterium incorporation commensurate with CTP-543's isotopic purity. As the '149 patent acknowledges, "a preparation of ruxolitinib will inherently contain small amounts of deuterated isotopologues." Appx1429(3:49-53). Trying to avoid anticipation by the "deuterated isotopologues" inherent in ruxolitinib, the '149 patent carefully defines several terms (including "deuterium" and "compound") to set a minimum level of deuterium incorporation encompassed by the claims. Appx1429(3:49-4:41); Appx6457-6464 ¶¶24-38. Under these definitions accepted by the Board, Appx11-12, all claims covering octa-deuterated ruxolitinib encompass mixtures with as much as 49.9% isotopologues that have hydrogen atoms at one or more of the positions designated "deuterium." And even for each designated "deuterium" position, the '149 patent only requires "at least 45%" deuterium isotopic

enrichment. Appx1429(3:41-4:3). This is far broader than the isotopic purity of CTP-543. Appx1429(3:60-4:36); *see also* Appx6465-6474 ¶¶39-56.

2. CTP-543's Flatter Pharmacokinetic Curve Is Neither Unexpected nor Significant

Concert contends that CTP-543's pharmacokinetic profile would have been "unexpected." Blue Br. 20-21. Concert's alleged results, however, are simply the predictable effect of slowing ruxolitinib's metabolism via deuterium substitution. Appx736-738. These expected effects of inhibiting metabolism were already known for deuterated compounds such as ivacaftor and venlafaxine. Appx1990-1991; Appx2815; *see also* Appx7907-7909; Appx5453-5455; Appx5725-5726(5:16-6:13); Appx5731(11:4-7). And reducing ruxolitinib's metabolism with a metabolic inhibitor had already been shown to increase half-life and AUC. Appx5465-5474; Appx5734-5740(14:1-20:5); Appx9173(87:7-22); Appx1713-1714; *see also* Appx9131-9133(45:21-47:2); Appx7907-7910. Moreover, the prior art taught negligible presystemic (i.e., "first-pass") metabolism for ruxolitinib—thus, no meaningful increase in C_{max} due to inhibition of presystemic metabolism would have been expected for deuterated ruxolitinib. Appx7865-7866; Appx7857-7867; Appx1729; Appx5860-5863(33:14-36:11); Appx1739; Appx5548-5549.

Concert tries to sidestep this predictability by reframing its alleged unexpected results as following the "flatter" "Tolerability/Efficacy" panel shown in the Concert Backgrounder as opposed to the "Bioavailability/Efficacy" panel.



Appx1739; *see also* Blue Br. 13-14, 20-23; Appx5548-5549; Appx5894(67:5-14); Appx5886-5895(59:7-68:7). According to Concert, a "flatter" profile with "about the same C_{max}"—which as explained above, would have been entirely expected—means that patients "taking CTP-543 would *likely* experience . . . 'comparatively fewer side effects,'" and that CTP-543 "*could* provide a significant clinical benefit." Blue Br. 21 (emphases added) (quoting Appx9385-9386 ¶38). But Concert's alleged benefits are entirely theoretical. There is no clinical data of record for CTP-543 in AA patients, much less any evidence of improved clinical efficacy over ruxolitinib. Appx35-37.

Undeterred, Concert makes up its own inapt comparisons to ruxolitinib. Blue Br. 20-21. For instance, Concert alleges that "CTP-543 has a longer half-life and

greater total exposure (AUC) *without* a statistically significant change in its maximum plasma concentration (C_{max})." Blue Br. 20. To get there, Concert compares 16 mg of CTP-543 to *27 mg* ruxolitinib. Appx6745-6748 ¶¶35-40; Appx7660-7663 ¶¶16-18; Appx7702-7703 ¶44; Appx739. But there is no evidence that 27 mg of ruxolitinib is required to effectively treat AA; to the contrary, 20 mg produced a "remarkable response" and was "well tolerated" in AA patients. Appx7824; Appx7828-7829; Appx6634-6635 ¶¶43-44. Indeed, inconsistent with its arguments in this proceeding, elsewhere Concert stated that 16 mg of CTP-543 twice daily ("BID") is "comparable to . . . the 20 mg BID ruxolitinib dose shown to be effective at inducing hair regrowth in patients with moderate to severe alopecia." Appx6825 ¶116. A 20 mg dose of ruxolitinib—a more appropriate comparison—would necessarily have a C_{max} lower than 27 mg. Concert's alleged results are simply an artifact of comparing CTP-543 to an unnecessarily high dose of ruxolitinib. Appx6745-6748 ¶¶35-40.

But even setting aside Concert's apples-to-oranges comparisons, the alleged unexpected results are an insignificant difference of degree that do not even *predict* a clinical benefit. Appx739-741. Concert reports that CTP-543 has a half-life of 3.3 hours, which is 0.4 hours longer than Concert's reported 2.9-hour half-life for ruxolitinib. Appx6636-6637 ¶¶47-50; Appx7656-7658 ¶12. And according to Concert, this difference translates to 14.9 hours in the "therapeutic window" for

16 mg of CTP-543 compared to 12.7 hours for 27 mg of ruxolitinib. Appx7661-7662 ¶17; Appx6749-6755 ¶¶44-50. Thus, even accepting Concert's data as true, CTP-543 would need to be dosed *twice daily* to provide a steady-state treatment for a full 24 hours—just like ruxolitinib. Appx6636-6637 ¶¶47-50; Appx9883 ¶33. With the second dose administered at 12 hours, the concentration of neither drug will dip below Concert's purported threshold of 50 nanomoles per liter. *Compare* Blue Br. 21, *with* Appx6749-6755 ¶¶44-50.

3. CTP-543's Effect on Rapid Metabolizers Is Neither Unexpected nor Significant

Concert characterizes a relatively greater increase in half-life for fast ruxolitinib metabolizers as "unexpected." Blue Br. 22. According to Concert, its "experts testified that they know of *no other reported instances* of this effect in a drug metabolized by the same enzyme as ruxolitinib," CYP450-3A4. *Id.* But Concert's declarant, Dr. Harbeson, admitted he was "aware of a similar occurrence, which is the case of deutero tetrabenazine[,] -- which is metabolized by [CYP450-2D6]," also a CYP450 enzyme, that had been reported. Appx5989-5991(70:4-72:8); Appx9683. Another deuterated drug metabolized by the same enzyme as ruxolitinib also showed the same effect. Appx6740-6745 ¶¶26-34; Appx6777-6782. Indeed, neither Concert nor its experts could identify a single example of a deuterated drug that did *not* have this allegedly disproportionate effect on rapid metabolizers. *See* Appx5978-5980(59:17-61:18); *cf.* Blue Br. 22-23.

More fundamentally, Concert's allegedly unexpected effect for rapid metabolizers is nothing more than a product of how it chose to present the data. Appx6731-6734 ¶¶11-17. While Concert asserts that rapid metabolizers may experience "a greater *relative* increase in half-life," Blue Br. 22 (emphasis added), it omits that its own data showed the same *absolute* increase. Appx6731-6734 ¶¶11-17. As Incyte's expert, Dr. Thisted, explained, the half-life of CTP-543 is extended by the same 0.4 hours for all patients, meaning that patients who metabolize the drug faster will necessarily see a greater *relative* increase in half-life. Appx6732-6740 ¶¶13-25. Dr. Thisted further testified that this effect was not surprising but instead predictable to "[a]nyone with a calculator." Appx11003(92:2-16); *see also* Appx10930(19:1-13); Appx10931-10932(20:20-21:8); Appx10947-10948(36:18-37:5).

Regardless, the alleged difference is insignificant and its effect speculative. *See* Appx6636-6637 ¶¶47-50. Concert again relies on its manufactured therapeutic window to conclude that "rapid metabolizers are *more likely* to benefit from a given dose of CTP-543." Blue Br. 22 (emphasis added). But there is no evidence that CTP-543 produced greater efficacy, fewer side effects, or any other clinical benefit in "rapid metabolizers." Appx34-37; *see also* Appx6733-6734 ¶¶16-17.

D. Procedural History

1. Incyte's Petition

Incyte's petition for *inter partes* review challenged all claims of the '149 patent on three grounds: (1) obviousness over the Jakafi® Label, Shilling, and the Concert Backgrounder; (2) anticipation by Rodgers; and (3) obviousness over Rodgers, Shilling, and the Concert Backgrounder. Appx124-125. Following Incyte's request for rehearing of the institution decision, the Board instituted review on all grounds. Appx2. After the parties' joint request, the Board subsequently limited the review to the obviousness grounds. *Id.*

2. The Board's Final Written Decision Holding All Challenged Claims Obvious

a. The Board Found that a Skilled Artisan Would Have Been Motivated to Deuterate Ruxolitinib

After determining that a skilled artisan would have selected ruxolitinib as a lead compound, Appx21, the Board weighed the evidence and found two independent reasons why a skilled artisan would have been motivated to modify ruxolitinib to achieve the claimed compounds: (1) to improve the ADME properties of ruxolitinib and (2) to obtain a compound with at least similarly desirable properties as ruxolitinib. Appx23-28.

Specifically, the Board found that a skilled artisan would have been motivated "to deuterate Rodgers's ruxolitinib compounds at their metabolic 'hot spots,' as

identified by Shilling, in the manner taught by the Concert Backgrounder to achieve the potential benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability, and efficacy." Appx23-24. The Board pointed to the fact that Shilling taught that ruxolitinib has well-identified sites of metabolism and credited Dr. Guengerich's testimony that the Concert Backgrounder taught that deuteration at these "metabolic hot spots" was reasonably predicted to improve ruxolitinib's ADME properties. Appx22-23; *see also* Appx11-12.

The Board rejected Concert's contention that a skilled artisan would have been dissuaded from slowing ruxolitinib's metabolism due to alleged concerns over toxic side effects. Appx24-25. The Board concluded that neither Concert nor Dr. Ortiz de Montellano had provided evidence that deuterating Rodgers's compounds would have been unattractive to a skilled artisan for fear of disturbing the chemical properties. Appx25. Rather, extensive evidence showed that a skilled artisan would have understood that side effects of ruxolitinib were dose dependent, and "the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug." Appx25-26; *see also* Appx9491; Appx5893(66:8-15). Citing Dr. Ortiz de Montellano's failure to consider this fundamental principle, the Board "assign[ed] little weight to his conclusion" that a skilled artisan would have been dissuaded from deuteration by dose-dependent side effects. Appx26.

Independent of the desire for improved properties, the Board also found that the skilled artisan would have been motivated by the expectation that the claimed analogs would have at least similar properties as ruxolitinib. Appx24; Appx27-28. The Board credited Dr. Guengerich's testimony—"supported by the Concert Backgrounder," Appx28—that deuterated compounds have "selectivity and potency comparable to their hydrogen analogs," and highlighted Concert's CEO's statement that "[a]t Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterated it.'" Appx23 (first quoting Appx152, and then quoting Appx2406). The Board also pointed to testimony from Concert's Dr. Harbeson that "any deuterated analog of ruxolitinib we would presume to retain the same intrinsic biology and pharmacology [as ruxolitinib]." Appx28 (quoting Appx6016(97:4-18)).

b. The Board Found that a Skilled Artisan Would Have Had a Reasonable Expectation of Success

The Board next turned to the issue of a reasonable expectation of success. Appx29-32. Crediting Dr. Guengerich's testimony, Appx29 (citing Appx1509-1510 ¶¶104-105), the Board found that a skilled artisan would have had a reasonable expectation of successfully deuterating ruxolitinib compounds at their metabolic "hot spots" identified by Shilling, in the manner taught by the Concert Backgrounder. Appx29-31. Concert did not argue otherwise. Appx30.

While noting that the challenged claims do not recite any specific changes to ruxolitinib's pharmacokinetic profile, Appx31, the Board went even further, confirming that "a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs 'may display' superior ADME properties," as explained in the Board's "discussion of a motivation to combine." Appx31-32; *see also* Appx23-28. The Board additionally found that a skilled artisan would have had "an expectation that the claimed and prior art compounds would have similar properties, in general." Appx28.

c. The Board Found Concert's Purported Objective Evidence Unavailing

The Board considered, and found unpersuasive, Concert's alleged unexpected results. The evidence showed that CTP-543's alleged "*increased time* in the therapeutic window" and "*increased clinical response* at a given dose" for rapid metabolizers are "at most" a difference in degree compared to ruxolitinib. Appx33-35 (citation omitted). The Board did not reach whether the results were commensurate in scope with the disputed claims, explaining that, "*[e]ven if commensurate in scope* and taken as true and unexpected, Patent Owner's asserted results for CTP-543 demonstrate an increase in the same clinical activity observed with ruxolitinib." Appx35 (emphasis added); Appx51.

Concert had also repeatedly alleged a highly specific "long-felt need for an *FDA-approved* treatment for AA." Appx1086 (emphasis added); *see also*

Appx465-466; Appx1365-1367(59:17-61:11); Blue Br. 19-20 (relying on FDA "Fast Track" designation). But Concert's assertion that CTP-543 has satisfied this alleged long-felt need was "unsupported." Appx36. The Board found that Concert had continuously described CTP-543 as a "'potential' treatment of AA with a lower dose and fewer side effects." Appx36 (quoting Appx498); *see also* Appx1365-1367(59:17-61:11). The Board found no record evidence—and Concert provided none—of CTP-543 actually having fewer side effects, being administered at a lower dose, or even being effective against AA, much less more effective against AA than ruxolitinib.

After considering Concert's alleged secondary considerations and all the factors outlined in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), the Board determined that the challenged claims are unpatentable as obvious under Ground 3 and therefore did not reach Ground 1. Appx37.

3. Concert's Appeal

Concert appealed to this Court. Following the Supreme Court's decision in *United States v. Arthrex, Inc.*, 141 S. Ct. 1970 (2021), this Court granted a limited remand for Concert to request Director Review. Dkt. No. 56. Concert's petition was denied. Appx54-55.

SUMMARY OF THE ARGUMENT

This Court has explained that obviousness of a chemical compound "may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound." *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009). Concert concedes that, as a matter of law, this standard applies. Blue Br. 33; Appx480-481. And Concert concedes, as a matter of fact, that "the expectation is that a deuterated drug will have similar pharmacodynamic properties as the protio drug." Appx482. The Board faithfully applied this precedent, weighed the parties' arguments and evidence, and determined that the challenged claims would have been obvious to a skilled artisan.

Notwithstanding its admissions of law and facts, Concert alleges that the Board "applied the wrong legal standard." Blue Br. 33. Concert's common theme is that alleged unpredictability in some chemical properties—i.e., the "effect on ADME properties or metabolic processes," Blue Br. 34—renders the claimed compounds nonobvious despite their expected similarities with ruxolitinib. For each alleged "legal" error, however, Concert either mischaracterizes the Board's analysis or misstates the law altogether. The reason behind Concert's attempt to manufacture legal error is simple—Concert cannot overcome the substantial evidence supporting each of the Board's findings. This Court should affirm.

Start with Concert's accusation that the Board applied an incorrect motivation standard that "ignored the pertinent properties of the deuterated compounds" and, "at best, provided a reason to deuterate *all* drugs." Blue Br. 33-34. That cannot be squared with the Board's extensive consideration of the totality of prior art—including statements from Concert itself—underscoring an expectation that deuterating ruxolitinib at its known metabolic hotspots would at least result in compounds with similar "selectivity," "potency," "biology," and "pharmacology." *See* Appx21-28; *see also* Appx2406; Appx1739; Appx6016(97:4-18).

Nor can it be squared with the Board's express consideration of pharmacokinetic properties and its independent finding that a skilled artisan would have expected that deuterating ruxolitinib at the primary metabolic hotspots along its cyclopentyl ring would potentially lead to *improved* safety, tolerability, and efficacy as described in the Concert Backgrounder. Appx23-28; Appx31-32. Hematological side effects in blood cancer patients predisposed to such issues would not have discouraged deuterating ruxolitinib for use in healthier subjects. But even if side effects arose, skilled artisans would have understood how to mitigate them through dose modification. Appx24-26. And none of Concert's other alleged concerns—metabolic switching, masking, or presystemic metabolism—would have deterred a skilled artisan. *See supra* Section A.2.b, Section C.3.

Concert also accuses the Board of ignoring unclaimed "pharmacokinetic properties" in addressing reasonable expectations. Blue Br. 34. The Board, however, correctly applied this Court's precedent requiring "a motivation to combine accompanied by a reasonable expectation of achieving *what is claimed* in the patent-at-issue." *Intelligent Bio-Systems*, 821 F.3d at 1367 (emphasis added); *see also* Appx29-33. None of the challenged claims here recite any pharmacokinetic properties. And there is no dispute that synthesizing the claimed compounds would have been within the skill in the art and routine. Appx30-31. But even applying Concert's erroneous standard, the Board also found—consistent with its motivation findings—that skilled artisans would have had "a reasonable expectation that the synthesized ruxolitinib analogs 'may display' superior ADME properties." Appx31-32; Appx22-28.

None of Concert's evidence showed that CTP-543 exhibits unexpected results or satisfies a long-felt, unmet need. Concert's contention that the Board's decision somehow makes "virtually *any* unexpected result into a difference in degree," Blue Br. 34-35, is plainly wrong. Considering the record evidence, the Board correctly determined that Concert's alleged "'increased time in the therapeutic window' and an 'increased clinical response at a given dose' for CTP-543 as compared to ruxolitinib are not of a 'kind.'" Appx34-35. And the Board did not find that CTP-543 failed to satisfy a long-felt, unmet need solely because it lacked FDA approval.

Blue Br. 35. Instead, the Board correctly found that Concert had not shown that CTP-543 actually satisfies a long-felt, unmet need by treating AA with a lower dose and fewer side effects. Appx35-37.

ARGUMENT

I. Standard of Review

Obviousness is a question of law based on underlying factual findings, including (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham*, 383 U.S. at 17-18; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 399 (2007).

This Court reviews the Board's factual findings for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000). "Substantial evidence . . . is 'more than a mere scintilla.' It means—and means only—'such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'" *Biestek v. Berryhill*, 139 S. Ct. 1148, 1154 (2019) (citations omitted). Where "two inconsistent conclusions may reasonably be drawn from the evidence in record, the [Board]'s decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence." *Knowles Elecs. LLC v. Iancu*, 886 F.3d 1369, 1374 (Fed. Cir. 2018) (citation omitted).

II. The Board Applied the Correct Motivation Standard and Its Findings Are Supported by Substantial Evidence

A. The Board Found Motivation to Deuterate Ruxolitinib Based on an Expectation of Similar Selectivity and Potency as Well as the Potential for Improved Safety, Tolerability, and Efficacy

Concert acknowledges that a motivation to create a claimed molecule from a prior-art compound can arise where there is "an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." Blue Br. 37 (quoting *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)). Applying this standard, the Board found that "the preponderance of the evidence supports Petitioner's assertion that a motivation to make deuterated ruxolitinib compounds and compositions exists based upon the structural similarity between those claimed compounds and the prior art compounds." Appx23-24 (citing Appx1477 ¶55; Appx2406); *see also* Appx27-28.

Concert does not challenge the substantial evidence underlying the Board's finding of "structural similarity" between the claimed deuterated compounds and prior-art ruxolitinib. As this Court has explained, "the greater the structural similarity between the compounds, the greater the motivation to combine and reasonable expectation of success." *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018). And the structural similarity could not be closer as "replacement of one or a few hydrogens in a drug molecule by deuterium" is "*the smallest structural change that can be made*" and "will have negligible steric

consequences or influence on physicochemical properties." Appx2919 (emphasis added).

Concert instead creates a straw man and proceeds to set it ablaze. According to Concert, the Board committed legal error by failing to address "whether a skilled artisan would be motivated by a belief that the claimed compounds shared *relevant* 'functional similarities' with ruxolitinib," Blue Br. 41 (quoting *Anacor*, 889 F.3d at 1385), and instead "*thought it enough* that deuterated compounds have the same structure and 'similar properties, in general,' to compounds containing hydrogen rather than deuterium," Blue Br. 40-42 (emphasis added) (quoting Appx28). But Concert misstates the Board's legal analysis and its findings. The Board considered "*relevant* 'functional similarities,'" Blue Br. 41 (quoting *Anacor*, 889 F.3d at 1385), and steadfastly followed this Court's instruction to evaluate structural obviousness "in light of the totality of the prior art." *Aventis*, 499 F.3d at 1301; Appx23-24; Appx27-28.

For instance, as Concert acknowledges, selectivity and potency are "two of a drug's important properties." Blue Br. 41. In finding that "the preponderance of the evidence supports Petitioner's assertion" that skilled artisans would have been motivated to make deuterated ruxolitinib based upon "structural similarity," Appx24, the Board relied on published statements from Concert's CEO explaining that, "[a]t Concert, 'we've *never* seen any biologically relevant differences in

target selectivity or potency of a drug when we deuterate it,'" Appx2406 (emphases added). *See also* Appx28. And the Board credited Dr. Guengerich's testimony that deuterium-substituted ruxolitinib compounds would have been expected to have selectivity and potency comparable to their hydrogen analog. Appx24 (citing Appx1477 ¶55); Appx28 (citing Appx1477 ¶55).

Similarly, the Concert Backgrounder relied upon by the Board would have confirmed for a skilled artisan that "[d]euterium-substituted compounds retain their molecular shape and thus have *selectivity and potency* comparable to their hydrogen analogs." Appx1739 (emphasis added); Appx28. And the Board further considered testimony from Concert's own declarant, Dr. Harbeson, who explained that "any deuterated analog of ruxolitinib *we would presume to retain the same intrinsic biology and pharmacology*." Appx28 (emphasis added) (quoting Appx6016(97:4-18)); *see Aventis*, 499 F.3d at 1301.

Concert does not challenge the Board's findings that skilled artisans would have expected ruxolitinib and its deuterated analogs to share the "important properties" of selectivity and potency. Blue Br. 41; *see also* Blue Br. 30, 54; Appx28. In fact, Concert admits—as it must—that "[b]ecause hydrogen and deuterium are almost identical in size and shape, deuteration typically has *little or no effect on a drug's selectivity and potency*," Blue Br. 7 (citing Appx1739), and that "[d]euterium-substituted compounds retain their molecular shape and thus

have selectivity and potency comparable to their hydrogen analogs," Blue Br. 27 (alteration in original) (quoting Appx1739). This important nexus between "structural similarities" and "functional similarities" alone provides sufficient motivation to deuterate ruxolitinib at its metabolic hotspots. *Anacor*, 889 F.3d at 1385.

Nevertheless, Concert contends that the Board committed legal error "by focusing its motivation analysis on structural similarities like atomic size and molecular shape" while ignoring "the unpredictable effects of deuteration on the pharmacokinetic properties of ruxolitinib, especially those relevant *to the balance of safety and efficacy*." Blue Br. 40 (emphasis added). But Concert again disregards the Board's actual analysis. The Board independently found that skilled artisans would have been motivated to deuterate ruxolitinib "to achieve the potential benefits that the Concert Backgrounder disclosed, e.g., *improved safety, tolerability, and efficacy*." Appx23-24 (emphasis added); *see also* Appx27; Appx31-32. That is, exactly contrary to Concert's allegations, the Board *did* consider the effects of deuteration on pharmacokinetic properties relevant to safety and efficacy. And the Board's findings in this regard are supported by substantial evidence. *See supra* Section A.1, Section A.2; *see infra* Section II.C.

At bottom, the Board considered extensive "evidence demonstrating a nexus between structural similarities" and "functional similarities," *Anacor*, 889 F.3d at

1385—including selectivity, potency, safety, tolerability, and efficacy—cementing an expectation that deuterated ruxolitinib compounds would perform *at least* as well as their hydrogen analog. Appx21-28; *see also* Appx1503-1509 ¶¶91-103.

B. The Board Found that a Skilled Artisan Would Have Pursued the Specific Modifications Claimed in the '149 Patent

Concert also alleges that the Board "failed to ask whether a skilled artisan would have pursued the specific modifications claimed in the '149 Patent." Blue Br. 45-48 (emphasis omitted). The Board, however, carefully considered this very issue, finding that Incyte had "shown persuasively how a person of ordinary skill in the art would have understood from Shilling that Rodgers's ruxolitinib compounds feature the metabolic 'hot spots' targeted by the Concert Backgrounder for deuteration." Appx27 (citing Appx153; Appx172-176); *see also* Appx11-12; Appx21-24; Appx50; Appx1500-1502 ¶¶83-87. Concert's mere disagreement with the Board's factual conclusions does not provide any reason to disturb them on appeal. *See Knowles Elecs.*, 886 F.3d at 1374.

The Board's finding that a skilled artisan would have been motivated to create the claimed ruxolitinib compounds with tetra- and octa-deuterated cyclopentyl rings is supported by substantial evidence directing skilled artisans to deuterate at positions where the parent molecule is metabolized. *See supra* Section A.2.b; *see also* Appx1489-1491 ¶¶68-70; Appx1500-1502 ¶¶83-88. The Concert Backgrounder highlighted the well-known strategy of targeting a compound's

"[m]etabolic 'hotspots'" with deuterium substitution to improve "safety, tolerability and efficacy." Appx1739-1741; *see also* Appx1492-1500 ¶¶74-82; Appx27; *see supra* Section A.2.b. Making ruxolitinib particularly suitable for this strategy, Shilling reported that the vast majority of ruxolitinib's metabolism occurred at the four methylene carbons on its cyclopentyl ring—its hotspots. Appx1733-1736; *see also* Appx1489-1491 ¶¶68-70; Appx1500-1502 ¶¶83-87.

Moreover, the specific metabolic reaction at ruxolitinib's hotspots—hydroxylation of the cyclopentyl ring methylene carbons—would have been expected to produce a significant and beneficial KIE when deuterated. Appx1472-1473 ¶50; Appx1504-1509 ¶¶94-103; Appx1739-1740; Appx9133(47:9-17); *see also supra* Section A.2.b, Section C.2. While the claimed octa-deuterated compound would have been expected to produce the largest KIE because it inhibited metabolism at all four hotspots, the claimed tetra-deuterated compounds would have been expected to produce KIE as well. Appx1501-1502 ¶¶86-87; Appx1741-1742; *see also* Appx11-12; Appx22-23.

Concert's reliance on *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006), and *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009), is misplaced. Blue Br. 45. In *Sanofi-Synthelabo*, this Court affirmed a district court's validity findings where "*nothing* directed a chemist" to the "particular enantiomer and salt" at issue. 470 F.3d at 1379

(emphasis added). And in *Procter & Gamble*, this Court affirmed the district court's validity findings where there was "*no credible evidence* that the structural modification was routine." 566 F.3d at 997 (emphasis added).

Unlike both cases, the Board here found the challenged claims invalid where the prior art would have directed skilled artisans to routine deuterium substitutions at specific locations—"specific molecular modifications," *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (citation omitted)—and further taught how those specific modifications had the potential to improve safety, tolerability, and efficacy. Appx27 (citing Appx153; Appx172-176); Appx1739-1742; *see infra* Section II.C. And, as the Board found, Concert did "not contend that such a structural modification would not have been within the skill in the art and routine." Appx29-31.

Concert's attempt to recast the Board's findings as a generalized "reason to *deuterate all drugs*, based on the *potential* to create something new and valuable," also goes nowhere. Blue Br. 47. Regardless of whether all sites of metabolism are ideal targets for deuteration generically, *see* Appx1504-1505 ¶95; Appx9324-9327(238:9-241:8), the Board detailed how ruxolitinib in particular "contained well-identified sites of oxidative metabolism in *in vivo* metabolism, as shown in Shilling," Appx23-24 (quoting Appx176)—the very "metabolic 'hot spots' targeted by the Concert Backgrounder for deuteration," Appx27; *see also*

Appx1474-1476 ¶53. This was more than sufficient to support the Board's finding with respect to the claimed compounds *specifically*.

C. The Board Rejected Concert's Reliance on Unpredictability and Found that Skilled Artisans Would Not Have Been Discouraged from Deuterating Ruxolitinib

Concert further alleges that "the Board ignored the *unpredictable* effects of deuteration on the pharmacokinetic properties of ruxolitinib, especially those relevant to the balance of safety and efficacy." Blue Br. 40 (emphasis added). Yet at the same time, Concert inconsistently argues that the *predictable* effects of slowed metabolism would have "discouraged" skilled artisans "from deuterating ruxolitinib given what was known about ruxolitinib's dose-dependent toxicities." Blue Br. 33. Despite this contradiction, Concert's ultimate point appears to be that the alleged need to empirically verify the pharmacokinetic properties of deuterated ruxolitinib compounds *in vivo* precludes obviousness as a matter of law. *See id.* ("Applying the proper test, the Board never would have found motivation . . . ."). Not so—this Court has explained that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364.

Concert's attempt to portray the Board's decision as disregarding the "unpredictability" of unclaimed properties simply rehashes factual disputes that the Board already resolved in Incyte's favor based on substantial evidence.

See Appx31-32 (rejecting Concert's "unpredictability" arguments). "This [C]ourt does not reweigh evidence on appeal, but rather determines whether substantial evidence supports the Board's fact findings." *In re NTP, Inc.*, 654 F.3d 1279, 1292 (Fed. Cir. 2011).

As discussed above, the Board *did* consider the expected effect of deuteration on pharmacokinetics and found that the totality of the prior art would have provided a skilled artisan "a reason to deuterate Rodgers's ruxolitinib compounds at their metabolic 'hot spots,' as identified by Shilling, in the manner taught by the Concert Backgrounder to achieve the potential benefits that the Concert Backgrounder disclosed, e.g., *improved safety, tolerability, and efficacy*." Appx23-24 (emphasis added); *see also* Appx27. What's more, the Board expressly found that "a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs 'may display' *superior ADME properties*." Appx31-32 (emphasis added). Concert's factual disagreement notwithstanding, this motivation was sufficient—after all, "absolute predictability of success" is not required. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); *see also Pfizer*, 480 F.3d at 1366; *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1075 (Fed. Cir. 2015) (obviousness requires considering whether "the hypothetical skilled artisan would recognize the *potential benefits* and pursue the variation" (emphasis added)).

The Board's findings that Concert's alleged unpredictability would not have discouraged a skilled artisan from deuterating ruxolitinib at its metabolic hotspots is supported by substantial evidence, including, *inter alia*, the Concert Backgrounder, Shilling, and the testimony of Incyte's expert, Dr. Guengerich. Appx21-32. For instance, rather than discouraging, the Concert Backgrounder would have provided an encouraging blueprint for deuterating compounds such as ruxolitinib. Immediately after acknowledging that some testing may be necessary, the Concert Backgrounder directs persons of ordinary skill to deuterate "drugs with known efficacy and safety that address clinically validated targets," allowing one "to *rapidly create* novel, differentiated compounds" with "*substantially reduced R&D risk, time and expense*." Appx1740 (emphases added); *see also* Appx1491-1500 ¶¶71-82; Appx22-23; Appx29-30. And it further instructs skilled artisans to look at compounds with "[m]etabolic 'hotspots' . . . identified from literature reports of *in vivo* metabolism." Appx1741; *see also* Appx1492 ¶74; Appx153-154; Appx27; Appx30 (recognizing that "Dr. Guengerich considers the deuteration strategy disclosed in the Concert Backgrounder to be somewhat predictable" (citing Appx1495-1496 ¶77)).

Ruxolitinib was just such a compound ripe for deuteration as described in the Concert Backgrounder; it was already validated as an FDA-approved treatment for myelofibrosis and was also known to be effective against autoimmune conditions

such as AA. Appx20-21; *see also supra* Section A.2.a; Appx6625-6629 ¶¶18-29; Appx1488 ¶64. Shilling told a skilled artisan exactly where to focus for ruxolitinib—the promising metabolic "hotspots," Appx1741, on its cyclopentyl ring. Appx27; Appx29; *see also supra* Section A.2.b, Section II.B; Appx1733-1736; Appx1741. And skilled artisans would have expected that deuteration at these specific sites would slow metabolism. Appx1740-1742; Appx1500-1509 ¶¶83-103.

None of Concert's alleged generic "sources" of unpredictability apply here to dissuade from deuterating ruxolitinib specifically. Blue Br. 42-43. "[M]etabolic switching" sometimes observed in *other systems*, Blue Br. 43, would not have been a concern for ruxolitinib given its specific pattern of metabolism described by Shilling. *See supra* Section A.2.b; Appx1510-1511 ¶106. And while potentially relevant for *other systems*, no factors would have been expected to "mask" an *in vivo* KIE for tetra- and octa-deuterated ruxolitinib analogs specifically. *See supra* Section A.2.b.

As for Concert's argument that "dose-dependent side-effects" would have discouraged skilled artisans from deuterating ruxolitinib, Blue Br. 43-44, Concert inconsistently assumes that skilled artisans would have expected the very result that it tries to portray as unpredictable—that deuterating ruxolitinib's metabolic hotspots would slow metabolism. *See also* Appx474. Concert's argument is also

irreconcilable with *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738-39 (Fed. Cir. 2013), where this Court considered and rejected the patent owner's nearly identical argument that dose-dependent side effects taught away from increased dose. As was the case there, there is no evidence that deuteration "would be unproductive," "that the side effects would be serious enough to dissuade the development," or that "criticize[d], discredit[ed], or otherwise discourage[d] investigation into the invention claimed." *Id.*; *see also* Appx26-27.

In any event, the Board considered Concert's argument that "ruxolitinib's dose-dependent toxicity would have dissuaded [skilled artisans] from trying to change the metabolic profile via deuteration," Appx24-25 (quoting Appx475), "assign[ed] little weight" to the testimony of Concert's declarant (Dr. Ortiz de Montellano) on this point, Appx26, and ultimately found against Concert on the facts. *See* Appx24-26. It further found that a skilled artisan would have recognized that such "events rarely led to treatment discontinuation"—even for myelofibrosis patients who were predisposed to hematological side effects—and were "managed by a dose adjustment." Appx25 (quoting Appx9491); *see also supra* Section A.2.a. Because Concert's expert, Dr. Ortiz de Montellano, did not address this well-understood method of controlling dose-dependent side effects, the Board correctly assigned his motivation opinions "little weight." Appx25-26 (citing Appx5893(66:8-15)).

According to Concert, reducing the dose of a deuterated drug in response to dose-dependent side effects would have been an "unsatisfactory tradeoff" and "self-defeating at best." Blue Br. 44. The Concert Backgrounder, however, expressly encouraged deuterating known drugs at their metabolic hotspots to provide "[b]etter tolerability through *reduction of overall dose* and C_{max}." Appx1739-1741 (emphasis added); *see also* Appx14; Appx1742. Consistent with this encouragement, the Board correctly found that "the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug." Appx25-26.

Concert also attempts to portray *Sanofi-Synthelabo* as equating unpredictability with obviousness. Blue Br. 38-39, 41-42. But this Court simply affirmed the district court's "factual findings" reflecting the absence of motivation to separate enantiomers that "often possess *substantially different physiological properties* in comparison to each other." *Sanofi-Synthelabo*, 470 F.3d at 1378-80 (emphasis added).

Nothing in *Sanofi-Synthelabo* precludes an obviousness finding simply because an unclaimed property—even if a "*motivating*" property, Blue Br. 42—may have some unpredictability. To the contrary, "a rule of law equating unpredictability to patentability" every time a property needs verification through testing "cannot be the proper standard." *Pfizer*, 480 F.3d at 1364 (new salts of

known compound not separately patentable "simply because the formation and properties of each salt must be verified through testing"); *see also id.* at 1366 (distinguishing *Sanofi-Synthelabo*). Thus, it is of no moment if "the magnitude and nature of the deuterium benefit cannot be predicted *a priori*," Blue Br. 27 (quoting Appx1740), and that testing may be used "to identify those [deuterated compounds] that are differentiated," Appx14 (quoting Appx1740). *See also PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1363-64 (Fed. Cir. 2007) ("Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention.").

Concert's reliance on *Procter & Gamble* is similarly unavailing. Blue Br. 39-40. In that case, this Court affirmed the district court's finding that Teva had failed to show that risedronate would have been obvious over a prior-art compound called 2-pyr EHDP. *Procter & Gamble*, 566 F.3d at 993-97. While both compounds were bisphosphonates, the district court relied on contemporaneous authority that "every compound, while remaining a bisphosphonate, exhibits *its own physical-chemical, biological and therapeutic characteristics*, so that each bisphosphonate has to be considered on its own." *Id.* at 996 (emphasis added) (citation omitted). And the proposed modification entailed relocating functional groups, changing the compound's "three dimensional shape, charge distribution and hydrogen bonding properties." *Id.* at 995. Even more, the district court

determined that there was "*no credible evidence* that the structural modification was routine." *Id.* at 995-97 (emphasis added).

That is opposite of the established expectation here with routine deuterium substitution at ruxolitinib's metabolic hotspots—"the smallest structural change that can be made." Appx2919. As Concert acknowledges, hydrogen and deuterium "are almost identical in size and shape," Blue Br. 7 (citing Appx1739), and skilled artisans would have expected "[d]euterium-substituted compounds to retain their molecular shape and thus have selectivity and potency comparable to their hydrogen analogs," Blue Br. 27 (quoting Appx1739). *See also* Appx21-28; Appx30; Appx2406; Appx1739-1741; Appx6016(97:4-18); Appx1477 ¶55; Appx1503 ¶92 (noting that the claimed deuterated analogs "would have been expected to possess at least a similar efficacy and safety profile to that of ruxolitinib"). To the extent relevant here, *Sanofi-Synthelabo* and *Procter & Gamble* stand for the proposition that this Court does not substitute a factfinder's reasonable interpretation of the record with another party's preferences.

III. The Board Applied the Correct "Reasonable Expectation of Success" Standard and Its Findings Are Supported by Substantial Evidence

A. The "Reasonable Expectation of Success" Inquiry Focuses on the Claimed Invention

None of the challenged claims recite any pharmacokinetic properties. Appx31. Nor does the '149 patent disclose data showing the effect of deuteration on

ruxolitinib's *in vivo* pharmacokinetics. *See supra* Section B. Yet Concert contends that the "reasonable expectation of success" inquiry should focus on something more than what the claims require and more than what the patent discloses—whether a skilled artisan would have expected that deuterating ruxolitinib would provide "advantageous pharmacokinetic properties." Blue Br. 48-51. According to Concert, the Board erred by considering "whether a person of ordinary skill in the art would have had a reasonable expectation of successfully making the *claimed invention* in light of the prior art." Appx31 (citing *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009)); *see* Blue Br. 48-51.

But Concert conflates two different inquiries: *motivation to combine* and *reasonable expectation of success*. As this Court explained in *Intelligent Bio-Systems*, the former considers the rationale for combining the prior art while the latter is specific to "achieving *what is claimed* in the patent-at-issue." 821 F.3d at 1367 (emphasis added). Although an unclaimed property may be relevant to the motivation-to-combine inquiry where it is the reason proffered for the motivation, unclaimed properties are "of no moment" to the separate "reasonable expectation of success" inquiry directed to "success *in meeting the claims*." *Id.* at 1367-68 (emphasis added) (holding that an expectation of achieving an unclaimed "quantitative deblocking" property was central to the premise underlying

petitioner's motivation argument but irrelevant to the "reasonable expectation of success" inquiry since the claims "do not require quantitative deblocking at all").

Concert makes no mention of *Intelligent Bio-Systems* and instead points to *Takeda*. Blue Br. 49-51. But nothing in *Takeda* expands the "reasonable expectation of success" inquiry beyond what is required by the claims. Rather, this Court simply affirmed the district court's finding on *motivation* where the defendant had failed "to identify *some reason* that would have led a chemist to modify a known compound in a particular manner." *Takeda*, 492 F.3d at 1357 (emphasis added). And while this Court discussed a "reasonable expectation" of reducing or eliminating toxicity, it did so in affirming the district court's finding that a skilled artisan "would not have been *prompted to modify*" the prior-art compound "to synthesize the claimed compounds." *Id.* at 1362 (emphasis added). That is, consistent with *Intelligent Bio-Systems*, *Takeda* considered an expectation of achieving unclaimed properties only in the context of *motivation* specifically relying on those properties. *Id.* at 1357, 1360-63.

DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., likewise only addressed motivation—specifically, whether the art "taught away" from "the very reason Medtronic proffers as to why it would have been obvious to combine [the references], viz., the creation of a rigid screw." 567 F.3d 1314, 1326-28 (Fed. Cir. 2009); *cf.* Blue Br. 54-55. Nothing in *DePuy Spine* expands the separate

"reasonable expectation of success" inquiry into unclaimed properties. The only relevance of *DePuy Spine* here is that the Board specifically considered and rejected Concert's arguments that skilled artisans would have been dissuaded from deuterating ruxolitinib. Appx24-28 (citing *DePuy Spine*, 567 F.3d at 1326); Appx31-32; *see supra* Section II.C.

The Board found—and Concert did not dispute—that the structural modifications required to make the claimed tetra- and octa-deuterated ruxolitinib compounds would have been within the skill in the art and routine. Appx30-31; Blue Br. 48-51. Nothing more was required for "a reasonable expectation of success of developing the *claimed invention.*" *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (emphasis added).

B. The Board Found that a Skilled Artisan Would Have Had a Reasonable Expectation that Deuterating Ruxolitinib Would Improve or at Least Retain Key Properties

Even if the "reasonable expectation of success" inquiry required the Board to determine whether a skilled artisan would have expected that deuterating ruxolitinib would achieve unclaimed properties—including "advantageous pharmacokinetic properties," Blue Br. 48—Concert still misses the mark as the Board answered this very question.

First, the Board determined—supported by substantial evidence—that a skilled artisan would have had a reasonable expectation that deuterated ruxolitinib

compounds would at least have properties similar to ruxolitinib. Appx27-28 (finding "persuasive" Dr. Guengerich's explanation that "deuterium-substituted compounds . . . have selectivity and potency comparable to their hydrogen analogs" (quoting Appx1477 ¶55)); Appx23-24; Appx32; *see also supra* Section II.A. That is, the Board found a reasonable expectation of success connected to a specific motivating factor—comparable "selectivity and potency." Appx28 (quoting Appx1477 ¶55); *see also* Appx23-24; Appx152-153. Concert itself concedes that "deuteration typically has little or no effect on a drug's selectivity and potency," Blue Br. 7, which are "two of a drug's important properties," Blue Br. 41. In fact, without any record clinical data for CTP-543 in AA patients, Concert itself relies on an *expectation* from ruxolitinib's demonstrated activity and efficacy in treating AA that CTP-543 would have similar results. *See infra* Section IV.B.2. This expected nexus between "structural similarities" and important "functional similarities"—which Concert ignores—is sufficient even under Concert's erroneous test. *Anacor*, 889 F.3d at 1385.

Second, the Board independently found that Incyte had "established by a preponderance of the evidence that a skilled artisan would have had a reasonable expectation that the synthesized ruxolitinib analogs 'may display' superior ADME properties, based upon the combined teachings of Shilling and the Concert Backgrounder." Appx31-32; *see also* Appx23-24 (finding "a reason to deuterate

Rodgers's ruxolitinib compounds at their metabolic 'hot spots' . . . to achieve the potential benefits that the Concert Backgrounder disclosed, e.g., improved safety, tolerability, and efficacy"); Appx27; *see supra* Section II.A. This finding links a reasonable expectation of success to a separate motivational objective—"the potential to create new chemical entities with improved safety, tolerability, and efficacy," and "potentially to obtain superior ADME properties." Appx153-154; Appx5; Appx23-24; Appx31-32.

Concert alleges that a skilled artisan's expectation that tetra- and octa-deuterated ruxolitinib "'may display' superior ADME properties," Appx31-32, would have been a "[m]ere hope[]" or "*abstract possibility* of success." Blue Br. 52-53. The Board, however, correctly rejected Concert's generic unpredictability arguments, Appx32, and instead found—based on substantial evidence—that skilled artisans would have had a reasonable expectation of success in light of ruxolitinib's *specific* metabolic properties. *See* Appx29-32; Appx23-28; *see supra* Section II.C, Section A.2.b.

Rather than a "[m]ere hope[]," Blue Br. 52-53, a "conservative analysis" found deuterium modification resulted in a KIE for approximately 79% of the more than 180 unique compounds on record. Appx6488 ¶99; *see also* Appx10573-10574(92:12-93:2); *cf. OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (finding that references provided "no more than hope" where

failure rate was "99.5%"). Ruxolitinib's specific metabolic properties—including hydroxylated metabolism at its methylenes—made a beneficial KIE even more likely for tetra- and octa-deuterated ruxolitinib. Appx1500-1502 ¶¶83-87; Appx1504-1509 ¶¶94-103; Appx1733-1736; Appx1739-1741; *see also* Appx21-23; *see supra* Section A.2.b. And skilled artisans knew from Rodgers, Shilling, and the Concert Backgrounder that ruxolitinib was an ideal target for deuteration. *See supra* Section A.2.b, Section II.B. None of Concert's alleged concerns—metabolic switching, masking, or dose-dependent side effects—would have undermined a skilled artisan's reasonable expectations of retained selectivity and potency and potentially superior ADME for deuterated ruxolitinib. Appx31-32; Appx23-38; Appx1739; *see supra* Section A.2.a, Section A.2.b, Section C.2, Section II.C.

Concert contends that the Board's decision somehow "undermine[s] innovation," "remove[s] predictability from the application of § 103," and threatens "countless new compounds with advantageous properties." Blue Br. 54-55. But that parade of horribles cannot be squared with the Board's meticulous findings of fact addressing not only why a skilled artisan would have been motivated to deuterate *ruxolitinib in particular* at its known metabolic hotspots—including a skilled artisan's expectation of achieving those motivating objectives—but also why a skilled artisan would have had a reasonable expectation of success in meeting the claims. Appx21-32; *see also supra* Section II.

Specifically, the Board considered and rejected Concert's attempt to avoid obviousness "'by a showing of some degree of unpredictability in the art' despite the reasonable probability of success supplied by the structural similarity between the compounds and the motivation provided by the cited prior art . . . ." Appx32 (quoting *Pfizer*, 480 F.3d at 1364); *see also supra* Section II.C. Instead, the Board found that skilled artisans would have reasonably predicted that applying the deuteration strategy outlined in the Concert Backgrounder to Rodgers's ruxolitinib compound at its metabolic hotspots identified by Shilling would have achieved a compound that retained ruxolitinib's key properties with potential improvements touted in the Concert Backgrounder. *See* Appx31-32; Appx23-24; Appx29-30 (citing Appx1495-1496 ¶77); Appx1503 ¶92.

That Concert disagrees with the Board on these findings of fact does not mean that the Board committed legal error or that its findings are not supported by substantial evidence. *In re O'Farrell*, 853 F.2d at 903 ("Obviousness does not require absolute predictability of success."); *Allergan*, 754 F.3d at 965 (requiring only a "reasonable expectation of success," not "guaranteed" success).

IV. The Board Applied the Correct Legal Standard for Secondary Indicia and Its Findings Are Supported by Substantial Evidence

According to Concert, the Board "erred in its consideration of," "fail[ed] to understand the nature of," and "refus[ed] to consider" its alleged secondary indicia. Blue Br. 55-56, 61-62. At its core, Concert's disagreement is with the Board's fact

findings, which Concert asks this Court to substitute with its own and *reverse*. *See* Blue Br. 66 (not seeking remand). This Court should deny Concert's requested relief not only because the Board's findings are supported by substantial evidence, but also because Concert fails to even address a necessary predicate, viz., that its alleged secondary considerations are commensurate in scope with the disputed claims.

A. CTP-543's Alleged Results Are Neither Unexpected nor Significant

1. Concert's "Therapeutic Window" Is an Expected Difference in Degree and Insignificant

Concert alleges that "relative to ruxolitinib," CTP-543 unexpectedly "maintains drug levels within the desired therapeutic window for a longer period of time" without "a meaningful increase in C_{max}." Blue Br. 56. The Board, however, considered the entire record and found that Concert's purported difference was "not of a 'kind' so as to support a finding of nonobviousness of the challenged claims." Appx33-36. That finding is supported by substantial evidence establishing that CTP-543's allegedly longer therapeutic window is not a significant improvement over ruxolitinib. *See* Appx6745-6755 ¶¶35-50. For example, as Drs. Shapiro and Thisted testified, both drugs—CTP-543 and ruxolitinib—would need to be dosed twice daily to provide a steady-state treatment. Appx6636-6637 ¶¶47-50; Appx6749-6755 ¶¶44-50; *see also supra* Section C.2; Appx739-741.

With the second dose administered at 12 hours, they are both always within the "therapeutic window." *Compare* Blue Br. 21, *with* Appx6749-6755 ¶¶44-50.

The Board did not, as Concert alleges, take *Galderma* to mean that differences in degree are "*categorically* irrelevant." Blue Br. 57-58. Nor did it read *Galderma* to mean that results expressed as a percentage change—such as Concert's "5000%" hyperbole—are per se irrelevant. Blue Br. 58-59. Instead, the Board correctly found on the facts that Concert's alleged "'increased time in the therapeutic window' and an 'increased clinical response at a given dose' for CTP-543 *as compared to ruxolitinib* are not of a 'kind' so as to support a finding of nonobviousness of the challenged claims." Appx35 (emphasis added). That is entirely consistent with *Galderma*, where the failure of an expected percent increase in the prevalence of certain side effects to materialize was "only a difference in degree from the prior art results." 737 F.3d at 739.

Orexo AB v. Actavis Elizabeth LLC, 903 F.3d 1265 (Fed. Cir. 2018), is inapposite. *See* Blue Br. 58-59. In that case, a "66% improved bioavailability" was a difference in kind where the prior-art formulations were known to have poor bioavailability and there was *no* evidence that a skilled artisan would have expected the increase. *Orexo*, 903 F.3d at 1267, 1274; Blue Br. 58-59. Here, however, substantial evidence showed that Concert's alleged 0.4-hour increase in

half-life for CTP-543 over ruxolitinib was clinically insignificant—and entirely expected. *See supra* Section C.2.

Concert's alleged "safer profile for an entirely new condition, AA," Blue Br. 59, fails for another reason—it is entirely theoretical. *See supra* Section C.2; Blue Br. 21. There is no clinical data of record for CTP-543 in AA patients. Appx35-37. Nor is there any clinical data of record comparing CTP-543 to ruxolitinib in AA patients, much less showing that CTP-543 is unexpectedly safer than ruxolitinib. Instead, the data that Concert and its Amicus now attempt to inject shows that the efficacy and side-effect profile of CTP-543 in AA patients is nearly identical to that of ruxolitinib. *See infra* Section IV.B.2.

What's more, Concert's alleged "safer profile" for CTP-543 without a "meaningful increase in C_{max}," Blue Br. 56-59, is simply the *predictable* result of manipulating existing data and changing a single value in a mathematical model (i.e., inflating the dose of ruxolitinib to 27 mg). Appx6745-6748 ¶¶35-40; *see also* Appx7865-7866 (teaching negligible presystemic metabolism for ruxolitinib); Appx1729; Appx5860-5863(33:14-36:11); Appx1739; Appx5548-5549; *see supra* Section C.2. And Concert's alleged "flatter pharmacokinetic curve," Blue Br. 56, would have been *expected*—it was taught and even illustrated in the art, had been observed for deuterated versions of ivacaftor and venlafaxine, and would have

been expected for deuterated ruxolitinib in particular. *See supra* Section C.2; Appx1739-1742; Appx5548-5549.

2. The Effect of Deuteration for Rapid Ruxolitinib Metabolizers Was Entirely Predictable and Ultimately Insignificant

Concert alleges that "patients with the *shortest* half-life for ruxolitinib" (i.e., rapid metabolizers) "demonstrated the *greatest* relative increase in half-life with CTP-543," and that this result was "unexpected" because it was "not known in the prior art." Blue Br. 61. But Concert is wrong on both points. It was both *known* and *predictable* to "[a]nyone with a calculator." Appx11003(92:2-16); *see also supra* Section C.3. And, having considered Concert's evidence, the Board found that it "demonstrates, at most, results that differ in degree over the results observed with the closest prior art, rather than in kind." Appx34-35.

Concert represented to the Board that its declarants were "*not aware of another* example . . . [of] an inverse relationship between the magnitude of half-life improvement and the half-life for the non-deuterated drug." Appx464 (emphasis added). Yet Concert's declarant, Dr. Harbeson, admitted he was "aware of a similar occurrence" in the CYP450 metabolism of deuterotetrabenazine (Austedo™) reported in "public corporate presentations" from several years ago available "on the Web." Appx5989-5991(70:4-72:13); *see also supra* Section C.3; Appx741-743. Dr. Harbeson also submitted data for another compound showing

exactly the same trend. Appx8107-8108; Appx6741-6745 ¶¶27-34; Appx5999-6004(80:6-85:22).

What's more, even if Concert's experts "kn[e]w of *no other reported instances*" of the inverse relationship, Blue Br. 22, their *lack of knowledge* fails to establish what a "skilled artisan would have expected," *id*. Indeed, neither Concert nor its experts could identify a single example of a deuterated drug that did *not* have the allegedly unexpected inverse trend. Appx5978-5980(59:17-61:18); *see Forest Lab'ys, LLC v. Sigmapharm Lab'ys, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (holding that skilled artisans "could not have been surprised that the sublingual route of administration did not result in cardiotoxic effects" because skilled artisans would not have known "that *other routes* of administration *do* result in cardiotoxic effects" (emphases added)). Concert's argument thus "must fail" because it is "devoid of *any* evidence of what the skilled artisan would have expected." *Pfizer*, 480 F.3d at 1371; *see also supra* Section C.3.

According to Concert, the Board "fail[ed] to capture both the nature and importance of the unexpected benefit for more rapid metabolizers." Blue Br. 61-62. But there was no benefit of any import to have captured. Even if rapid metabolizers did "remain within the therapeutic window longer" as Concert alleges, *id.*, there is no evidence that the de minimis variations in half-life between patients would even be an observable—much less significant—clinical response.

Appx6733-6734 ¶¶16-17; *see supra* Section C.3; *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (differences from prior art must be "unexpected *and significant*" (emphasis added)).

At bottom, the Board was entitled to weigh the evidence (including Concert's lack of supporting evidence) and determine that any "*increased time* in the therapeutic window" for rapid metabolizers was only a "difference in degree" "when compared to the closest prior art." Appx34-35 (quoting Appx495).

B. CTP-543 Does Not Satisfy Any Long-Felt Need

There is no dispute that "AA is a serious autoimmune disease that causes hair loss and often leads to significant psychological distress." Blue Br. 63; *see also* Amicus Br. 2. But by June 2012, skilled artisans understood that JAK inhibitors, including previously FDA-approved ruxolitinib, were effective against AA. *See supra* Section A.2.a. A patent originating from Columbia University detailed the mechanistic underpinnings of JAK inhibition to treat AA, disclosed the use of ruxolitinib to treat AA, and disclosed the successful use of ruxolitinib and tofacitinib (another JAK inhibitor) in animal models. *Id.* Tofacitinib is routinely used in clinical practice for AA and, notably—as Concert admits—the FDA has approved JAK inhibitor baricitinib for AA. *Id.*; *see also* Appx6627-6628 ¶¶26-27; Blue Br. 18. Even independent of JAK inhibitors, Dr. Shapiro explained that there

were a range of other successful treatments for AA. Appx11279-11281(140:23-142:4); Appx11153-11155(14:4-16:10).

The Board considered and rejected Concert's argument that CTP-543 has satisfied a long-felt but unmet need for treating AA. Appx36. That finding is well supported by substantial evidence. Appx35-37.

1. Concert Repeatedly Argued to the Board a Long-Felt Need for an *FDA-Approved* Treatment for Alopecia Areata

Unable to credibly argue that CTP-543 satisfied a need to treat AA that was not already met by ruxolitinib, tofacitinib, and other prior-art treatments, Concert took a deliberately different tack before the Board. According to Concert, CTP-543 satisfied a highly specific "long-felt need for an *FDA-approved* treatment for AA." Appx1086 (emphasis added); *see also* Appx465 (arguing that "CTP-543 Satisfies the Long-Felt Need for an *FDA-Approved*, Evidence-Based Alopecia Areata Treatment" (emphasis added)). Before this Court, Concert and its Amicus continue pointing to potential FDA approval as a benchmark. Blue Br. 18-20, 62-63; Amicus Br. 2 ("[n]o FDA-approved AA treatment existed"), 16 ("We desperately need an FDA-approved treatment." (citation omitted)), 18-19 (FDA "fast track" status).

Notwithstanding Concert having defined the alleged need based on FDA approval, Concert and its Amicus accuse the Board of requiring "final FDA marketing approval" before any pharmaceutical compound can satisfy a long-felt

need. Blue Br. 63-65; *see also* Amicus Br. 9-11, 22-27. The Board did no such thing. *See infra* Section IV.B.2; Appx35-37. But even if the Board's decision had turned on CTP-543's lack of FDA approval, Concert and its Amicus cannot have it both ways. If the alleged need were an *FDA-approved* treatment for AA—as Concert has argued—CTP-543 has not yet met that need. Nor, if approved, will it be the first FDA-approved treatment for AA. *See* Blue Br. 18 (citing U.S. Food & Drug Admin., *FDA Approves First Systemic Treatment for Alopecia Areata* (June 13, 2022), https://bit.ly/3MP8dlS). If the alleged need were a treatment for AA, then ruxolitinib, tofacitinib, and other compounds had already met that need by "the filing date" of the '149 patent. *Procter & Gamble*, 566 F.3d at 998; *see also supra* Section A.2.a. Thus, however Concert frames the alleged long-felt need, CTP-543 falls short.

2. Concert's Submitted Evidence Relating to the "Potential" or "Likelihood" of CTP-543 Treating Alopecia Areata Does Not Demonstrate that It Satisfies a Long-Felt, Unmet Need

Concert represents that "the [Board's] sole basis for concluding that CTP-543 does not fulfill a long-felt need is that CTP-543 had not yet received final FDA marketing approval by the close of evidence." Blue Br. 63-64. But setting aside Concert's attempt to have its cake and eat it too, the Board considered Concert's argument "that CTP-543 *has satisfied* a long-felt but unmet need" and correctly

found it "unsupported" because Concert's proffered evidence only addressed the "'potential' or 'likelihood' of CTP-543 treating" AA. Appx36-37.

Indeed, because it lacked any clinical data for CTP-543 in AA patients, Concert was limited to arguing an *expectation* based upon ruxolitinib's demonstrated activity and efficacy in treating AA that CTP-543 would have *similar* results. Appx465; Appx482; Appx497-498; Appx7824-7832; Appx9377 ¶10; Appx9381 ¶25; Appx9383 ¶29; Appx9385-9386 ¶¶37-38; Appx9387 ¶¶40-41; *see also* Appx744; Appx1117; Appx36 (citing Appx9385-9386 ¶38). And at the oral hearing, counsel for Concert "candidly agreed" that its argument was based upon the "'likely efficacy' of CTP-543 to meet a need," and that "the FDA award of a Fast Track designation to CTP-543 indicates a 'likelihood' that CTP-543 'will fulfill the long-felt need and meet the secondary consideration.'" Appx36 (quoting Appx1366-1367(60:13-61:3)); *see also* Appx6783 (other compound granted "Fast Track" designation for AA); Appx6788 (same). The issue for the Board was not that CTP-543 lacked FDA approval; the issue was that Concert did not show that CTP-543 actually satisfied a long-felt, unmet need. Appx35-37.

Exposing the deficit of record evidence regarding CTP-543's actual performance, Concert and its Amicus improperly try to import additional material into the record. Amicus Br. 12-22. This Court's review, however, "is confined to the 'four corners'" of the record before the Board. *In re Watts*, 354 F.3d 1362,

1367 (Fed. Cir. 2004) (quoting *In re Gartside*, 203 F.3d at 1314); *see also Hughes v. SEC*, 174 F.2d 969, 974 (D.C. Cir. 1949) (holding that "unverified statements in the amici brief" from "outside the record in the instant case" did "not constitute grounds for overturning the decision" of the agency).

Regardless, none of the Amicus's newly introduced citations, Amicus Br. 12-19, change the fact that there was no unmet, long-felt need for CTP-543 to have met. By June 2012, JAK inhibitors—including ruxolitinib and tofacitinib—were recognized as being effective against AA. *See supra* Section A.2.a. And even if an unmet need did exist, the Phase 3 clinical data that Concert and its Amicus now attempt to inject into the record does not show that CTP-543 would have satisfied it; if anything, the data only underscores that the efficacy and side-effect profile of CTP-543 in AA patients is at best nearly identical to what has been reported for ruxolitinib in relevant patient populations. *Compare* Amicus Br. 19-22, *with* Appx6633-6637 ¶¶42-50; Appx7824-7832.

C. Concert's Alleged Secondary Indicia Are Not Commensurate in Scope with the Claims

Concert's secondary indicia arguments all rely on CTP-543, an octa-deuterated analog of ruxolitinib with a purported purity data isotopic purity. Appx9976 ¶10; Blue Br. 55-65. But because neither its octa-deuteration nor its isotopic purity is commensurate with the scope of the '149 patent's claims, *see supra* Section C.1, CTP-543 necessarily fails to support nonobviousness.

See Allergan, 754 F.3d at 965-66 ("[O]bjective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." (quoting *In re Tiffin*, 448 F.2d 791, 792 (CCPA 1971))).

Claim 1 covers *hundreds* of deuterated analogs, while claims 3, 4, 11, and 12 do not cover octa-deuterated ruxolitinib at all. Appx6452-6454 ¶¶13-16; *see also supra* Section C.1. Even the narrowest claim still encompasses three distinct compounds.[4] Appx6453-6454 ¶15; *see also supra* Section C.1. Concert cannot credibly assert that the specific octa-deuterated CTP-543 is representative of other differently deuterated ruxolitinib compounds covered by the claims—not after repeatedly asserting that the effects of deuterium vary on a species-by-species level. Appx477-478 n.12; Appx7720-7721 ¶75.

Moreover, no claim includes any deuterium incorporation limitation commensurate with CTP-543's specific isotopic purity. *See supra* Section C.1. Even the narrowest claims that cover octa-deuterated ruxolitinib still encompass mixtures where up to 49.9% of the compounds feature hydrogen atoms at one or more "deuterium" positions, and with as little as 45% deuterium isotopic enrichment at each "deuterium" position. *Id.* That is, the claims cover mixtures that include substantial amounts *of ruxolitinib* and other deuterated variations. Yet

[4] Because Concert has not argued secondary indicia separately for any claim, its alleged secondary indicia rise or fall with claim 1.

Concert has no evidence of anything "unexpected" in such mixtures. To the contrary, as Concert's declarant, Dr. Baillie, explained, "if [there is] a low enrichment, then any potential isotype effect would be diminished." Appx5802-5803(82:17-83:25).

Concert did not address whether CTP-543 is commensurate in scope with the disputed claims in its opening brief. And while the Board declined to make an express finding on this issue, Appx35; Appx51, Concert did not ask for a second opportunity via a remand to address whether CTP-543 is commensurate in scope. Because the only conclusion supported by substantial evidence is that CTP-543 is *not* commensurate in scope, this Court should also affirm on this basis. *Cf. Corning v. Fast Felt Corp.*, 873 F.3d 896, 901-02 (Fed. Cir. 2017) (declining to remand "where only one answer is supported by substantial evidence and there is neither a request nor an apparent reason to grant a second record-making opportunity").

V. This Court's Precedent Forecloses Concert's Challenge to Director Review

Concert tacks onto its merits appeal a placeholder challenge to Mr. Hirshfeld's authority to consider and deny Concert's request for Director review. Blue Br. 65-66. This Court, however, has already thoroughly considered and rejected each of Concert's recycled arguments. *See Arthrex, Inc. v. Smith & Nephew, Inc.*, 35 F.4th 1328, 1332-40 (Fed. Cir. 2022); *see also* Intervenor Br. 1-4. The outcome should be the same here.

CONCLUSION

For the foregoing reasons, Incyte respectfully requests that this Court affirm the Board's Final Written Decision.

Date: October 6, 2022

Respectfully submitted,

/s/ Mark J. Feldstein
Thomas L. Irving
Mark J. Feldstein
Jason L. Romrell
C. Collette Corser
Drew D. Christie
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
901 New York Avenue, NW
Washington, DC 20001-4413
(202) 408-4000

J. Derek McCorquindale
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
1875 Explorer Street
Suite 800
Reston, VA 20190-6023
(571) 203-2700

Trenton A. Ward
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
271 17th Street, NW
Suite 1400
Atlanta, GA 30363-6209
(404) 653-6400

Attorneys for Appellee Incyte Corporation

CERTIFICATE OF COMPLIANCE

The foregoing brief complies with the relevant type-volume limitation of the Federal Rules of Appellate Procedure and Federal Circuit Rules because:

> The brief has been prepared using a proportionally spaced typeface and includes 13,866 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f) and Fed. Cir. R. 32(b).

Date: October 6, 2022

/s/ Mark J. Feldstein
Mark J. Feldstein